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NISSEN,T

EXAMINER	
ART UNIT	PAPER NUMBER
1802/1227	32

VICKI S. VEENKER
FISH & NEAVE
875 THIRD AVE.
NEW YORK, NY 10022

1805

DATE MAILED: Dec/1993

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/26/93 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 39-41, 43-48, and 52-77 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 49-51 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 39-41, 43-48, and 52-77 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

III. DETAILED ACTION

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The allowability and subsequent examiner's amendment indicated in the interview summary of Paper No. 31 is hereby withdrawn. Prosecution on the merits of the claims is in response to the Paper No. 29, filed 8/26/93. Any inconvenience to applicant is sincerely regretted.

17. Claims ~~39-54~~ 39-41, 43-48, and 52-77 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited DNA constructs for expression of a chimeric polypeptide which is a subunit of an immunoglobulin molecule. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Since applicants have not submitted any significant rebuttal in papers 15 or 16, rejections are maintained for reasons of record as stated in papers 5, 7, and 10, mailed November 29, 1988, May 24, 1989, and September 25, 1990, respectively.

In addition, the following rejection is made. The enablement rejection is necessitated by the evidence submitted in the 131 affidavit. The affidavit submits essentially 4 separate experiments in which antibody binding was obtained. Of these experiments, only the last, performed in paragraph 18 was successful. In fact, this experiment was only successful when a particular phosphate buffer was used. Therefore, in view of a showing that only 1 in 4 of the experiments are operative in the instant claims, the instant invention cannot be considered to be enabled for any and all non-producing cell lines.

Furthermore, undue experimentation would be required to practice the instant invention in view of the fact that the J558L cell line under went some unexplained mutation (see paragraph 18, lines 3 and following) which resulted the single chain loss mutant becoming a double chain loss mutant. Therefore, there is a reasonable likelihood that the expression of antibodies was a peculiarity of the mutation of the TAO 6 or 18 cell lines of the instant 131. Otherwise, the other cell lines would have worked also. Alternatively, the phosphate buffer may have been the reason no binding was obtained with the original TAO cell lines since alteration of the buffer is the element that resulted in the success of the last experiment. In short, the record is not completely clear as a result of the affidavit which was submitted to swear behind the Ochi reference of record. Therefore, applicants are invited to submit evidence which might clarify the aforementioned inconsistencies and enable the scope of the instant claims.

In the response filed 82/6/93 applicants submit a declaration from Dr. Morrison explaining that the reaction buffer or the poor quality of the analytical tool. Therefore, applicants conclude on page 9 of the pending response that

> "Because applicants successfully showed antigen binding with the PC column and with ELISA both before and after the suspected loss of expression of the transfected kappa chain, it is simply not the case ha only 1 of 4 experiments is operative in the instant claims."

"Therefore, applicants conclude that the claims are enabled for any and all mammalian cell lines.

These arguments have been considered but are not deemed persuasive. The fact that the analytical reagents were inaccurate has been considered but still does not overcome the record as it stands. The record currently shows substantial non-functional embodiments. The inventor's sworn statements to the contrary, the declaration of Dr. Morrison filed 8/26/93 merely contains a series of conclusory statements alleging enablement for all mammalian cells. Note specifically paragraphs 10-12 of the 8/26/93 Morrison declaration. Paragraph 12 states that "..there was no reasons to believe that J558L differed from other mammalian cells with respect to its ability to express its endogenous genes." Such a position is not correct. The class of mammalian cells is extremely diverse structurally. For example, CHO cells are ovarian cells which are quite different and therefore may not process the immunoglobulin genes properly. The COS cell line is a simian kidney cell line which again has a vast difference in morphology and consequently different processing characteristics. Moreover, the references cited in paragraph 12 all deal with the same cell types as the specification (myeloma). These cells are not considered indicative of success in mammalian cells as a whole because antibodies are endogenously produced in myeloma cells. This is not the case with the aforementioned CHO and COS cell lines. The structural dissimilarity combined with the lack of diversity in evidence with respect to such cell lines results in the lack of enablement. Thus, applicants have chosen the example most similar to the <u>in vivo</u> environment to justify the a diverse population of cells. Applicant's claims should be limited to lymphoid cell lines.

39-41,43-48, and 52-77

18. Claims ~~39-48 and 52-54~~ are rejected under 35 U.S.C. § 103 as being unpatentable over Cabilly (L,R, or 2A) or Boss (2b) in view of Gillies(S).

Applicant's arguments filed May 23, 1991 and March 25,1991 have been fully considered but they are not deemed to be persuasive.

Rejections are maintained for reasons of record, stated in papers 5, 7, and 10, mailed November 29, 1988, May 24, 1989, and September 25, 1990.

Applicant's arguments as set forth in paper 16, filed May 20, 1991, may be summarized as follows. Applicants argue that the prior art involving immunoglobulin production in mammalian cells does not demonstrate the certainty of functionally producing immunoglobulins where both immunoglobulin chains are exogenous to the host cell. Further traversal is made with respect to the inadequacy of the Cabilly references. Cabilly is alleged to be inadequate in several areas. First, applicants emphasize that the instant receptors are functionally produced and assembled in the host cell rather than reconstructed after the fact, as in Cabilly. Second, Cabilly fails to mention any of the attendant advantages of mammalian expression systems demonstrated by the instant invention. Third, the prior art shows that bacterial expression systems do not functionally assemble immunoglobulins. Finally, arguments are made comparing the lack of enablement of the Cabilly reference when compared with the instant specification. Final arguments deal with the removal of the Boss patent from the prior art as the publication date is after the filing of the first parent application.

As regards the possibility of producing two exogenous immunoglobulin genes in a cell which does not produce immunoglobulin, the argument is not persuasive because the Cabilly references provide just such a teaching. The teaching is, however, a bacterial teaching. Nonetheless, the prior art does indeed teach the production of two immunoglobulin chains which are exogenous to the host cell expression system. The only difference between the instant invention and the prior art is now the type of host cell.

The Gillies reference solves this problem. The Gillies reference fails to teach production of two exogenous immunoglobulin chains in a host system, but ample description and enablement is provided for the functional production of immunoglobulins in mammalian hosts. Given Cabilly's explicit suggestion of mammals, one of ordinary skill in the art would have had ample motivation to combine the teachings of the Cabilly reference with the attendant advantages known to result from mammalian cell expression.

In sum, the enablement of Gillies solves applicant's concern with the mere paper reference of Cabilly. Applicant's for enablement under §35 U.S.C. 112 are far more stringent than requirements for enablement under §35 U.S.C. 102/103. So, the law demands that applicant's specification be far more explicit than the prior art (In re Lukach, 169 USPQ 795; Chester v Miller, 15 USPQ2nd 1333).

Moreover, the elements of Cabilly which are lacking are in fact supplied by Gillies, therefore, the problems of functional assembly are solved as well as the attendant advantages of mammalian cell expression. Furthermore, applicants have provided evidence on pages 4 and 5 of paper No. 16, that immunoglobulin subunits were known to functionally assemble in mammalian expression systems. Therefore, the fact that one of skill in the art is specifically motivated by Cabilly to use mammalian systems and that mammalian systems were known to functionally express exogenous immunoglobulin, would render the instant invention obvious to one of ordinary skill in the art.

Finally, applicant's arguments concerning the date of the Boss reference are not considered persuasive because the claims at issue are not limited specifically to receptors that are not chimeric. Failure to specifically claim a broader embodiment is not equivalent to specifically excluding said broader embodiment. Therefore, the instant claims cannot be given the August 1984 priority because these claims read on material not disclosed in the original parent.

The arguments filed 1/27/92 with the two affidavits concerning the unpredictability of the instant yields are not persuasive because the rejection is maintained because no arguments have been presented which would establish why the unexpected yield of a single cell line would be predictive of all cell lines. The unpredictability of the art as delineated by applicants would certainly seem to support the undue nature of extrapolating the instant results to other cell lines. Essentially, the rejection is maintained because applicants have extremely broad claims to products disclosed in the prior art which applicants urge are patentable base on results of a single cell line. Applicants have not submitted arguments to buttress the statistical significance of their unexpected results. See Ex parte Gelles 22 USPQ 2nd 1318. Dr. Morrison's arguments in paragraph 10 of the 132 declaration of Paper No. 24, filed Jan. 24, 1992, are drawn to the discussion of the instant invention's distinctiveness over the prior art rather than the reasons for extrapolating the isolated unexpected results to all cell lines. Applicants are invited to clarify their position.

In the response filed 8/26/93, applicants argue that the endogenous exogenous approach was not expected to work, much less produce a large increase in yield over the prior art. The 8/26/93 Morrison declaration stated above is submitted as evidence of the statistical relevance of the claimed invention.

This argument is not considered persuasive. Applicants have made their comparison exclusively against the Cabilly patent. The Gillies patent provides a vast increase in yield with respect to

the Cabilly patent. Note especially the teaching of Gillies at col. 7, lines 44 and following where the reference teaches that expression levels comparable endogenous protein were achieved. While applicant's argument concerning the omission of Gillies with respect to double transfection are well taken, the fact remains that Cabilly teaches such a transfection. Therefore, the argued elements of patentability are disclosed in the prior art. In so far as the 8/26/93 Morrison declaration is concerned. The declaration merely makes conclusory statements concerning the applicability of the claimed yield to all mammalian cells. Note, for example, paragraph 8 which states "...[i]t is my opinion that the 32% yield is an underestimate of the amount of correctly assembled antibody....". Paragraph 9 goes on to state that the statistical significance is "certain" without providing any detail as to why. Moreover, this argument only makes comparison to the Cabilly reference, not Gillies. Therefore, applicants alleged unexpected results are not considered commensurate in scope with the claimed invention. Accordingly, the rejection is maintained.

19. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-1794. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
December 23, 1993

George C. Elliott
GEORGE C. ELLIOTT
PRIMARY EXAMINER
GROUP 1800